PAPER

Brief sympathetic blockade in patients with complex regional pain syndrome

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Background: Stimuli arousing sympathetic activity can increase ratings of clinical pain in patients with complex regional pain syndrome (CRPS).
Objective: To determine whether the increase in pain is mediated by peripheral sympathetic activity.
Methods: The effect of sympathetic ganglion blockade on pain evoked by a startle stimulus and cooling the forehead was investigated in 36 CRPS patients.
Results: Loss of vasoconstrictor reflexes and warming of the limb indicated that sympathetic blockade was effective in 26 cases. Before sympathetic blockade, pain increased in 12 of these 26 patients when they were startled. Pain increased in seven of the 12 patients and in another five cases when their forehead was cooled. As expected, pain that increased during sympathetic arousal generally subsided in patients with signs of sympathetic blockade. However, pain still increased in three of 12 of patients after the startle stimulus and in six of 12 of patients during forehead cooling, despite indisputable sympathetic blockade.
Conclusions: These findings suggest that stimuli arousing sympathetic activity act by a central process to exacerbate pain in some patients, independent of the peripheral sympathetic nervous system. This may account for the lack of effect of peripheral sympathetic blockade on pain in some CRPS patients.

> ''...the rustle of a paper or of a woman's dress, the sound of feet, the noise of a band, all appeared to increase his pain....he assured me that every strong moral emotion made him worse—anger or disappointment expressing themselves cruelly in the aching limb.'' (page 201)[1]

Seventy years after S Weir Mitchell's perceptive observations on patients with chronic pain after gunshot wounds,[1] Kirklin *et al* interviewed 49 soldiers with chronic limb pain after war injuries.[2] Loud noises (58% of cases) and emotional excitement (47%) aggravated pain, whereas it was usually somewhat alleviated by ''very quiet surroundings without any disturbing features'' (page 329). In fact, to Kirklin *et al*, post-traumatic pain that was unaffected by disturbances in the individual's environment was not ''true causalgia,'' and they noted little pain relief after sympathectomy in such patients.

We recently investigated the effect of sympathetic arousal on pain in 61 patients with complex regional pain syndrome (CRPS), most of whom developed chronic pain after a limb injury that did not involve obvious damage to a peripheral nerve trunk (CRPS type I, reflex sympathetic dystrophy).[3] Experimentally induced heat pain decreased during various sympathetically arousing tasks in normal controls; in contrast, ratings of CRPS pain increased in over 70% of patients during forehead cooling or after they were startled by a loud noise. Similarly, Baron *et al* reported that spontaneous pain and the spatial distribution of mechanical dynamic and punctate hyperalgesia increased during whole body cooling in a subgroup of CRPS patients.[4] In particular, hyperalgesia associated with sympathetic vasoconstrictor activity was greater in patients whose pain decreased after sympathetic blockade than in those whose pain remained unchanged. These observations suggest that sympathetic arousal, induced by various means, may heighten some of the features of CRPS.

Our aim in the present study was to determine whether peripheral sympathetic blockade would prevent increases in pain evoked by a startle stimulus and forehead cooling in patients with CRPS. Sympathetic vasoconstrictor neurones release noradrenaline during emotional excitement and body cooling.[5 6] As pain increases after subcutaneous injection of α adrenergic agonists in the symptomatic limb of certain patients with CRPS,[7–9] release of noradrenaline (norepinephrine) during sympathetic arousal may also be a source of pain. In fact, a plausible rationale for treating CRPS with sympathetic blockade is that it interrupts adrenergic excitation of a nociceptive impulse generator in the affected limb. Therefore, we hypothesised that sympathetic blockade would prevent increases in pain during forehead cooling and after a startle stimulus in patients with CRPS.

METHODS

Patients

The sample consisted of 12 men and 24 women aged between 15 and 68 years (mean 43 years) with pain or hyperalgesia in an arm (21 patients) or leg (15 patients), who were scheduled for diagnostic sympathetic blockade. Pain had begun after various forms of trauma and had persisted for between two weeks and 72 months (table 1). In two patients, electromyography and nerve conduction tests indicated peripheral nerve damage but pain and sensory abnormalities had spread outside the territory of the injured nerve (causalgia, CRPS type II). In another 19 patients, trauma from laceration, surgery, or electrocution probably involved some peripheral nerve damage but this was not investigated electrophysiologically. The remainder of the patients met criteria for CRPS type I (reflex sympathetic dystrophy).[10] In each case vasoconstrictor and electrodermal responses were detected in the affected limb before sympathetic blockade, indicating that the sympathetic nerves were grossly intact.

Each participant gave their informed consent for the procedures, which were approved by the Murdoch University human research ethics committee.

Table 1 Patient characteristics and response to sympathetic blockade

Patient No: Sex, age (years)	Type of injury	Duration of pain (months)	Response to sympathetic blockade: Pain ratings:before/ 1–3 h/7 h[a]	Temperature (°C)[b]: affected/unaffected		EDA[c]	VR[c]	Pain increase: before/ after block	
				Before	After			Startle	Cold
Patients with effective sympathetic blockade									
1: F, 46	R foot surgery	4	4/1/0	24/24	34/23	–	–	2/0	2/0
2: F, 63	L thumb surgery	2.5	6/3/3	25/25	35/32	–	–	2/0	0/0
3: M, 30	L ankle inversion	3	5/1/1	23/25	35/25	–	0	1/0	1/0
4: M, 49	R shoulder sprain, surgery	5	5/2/2.5	33/31	34/31	–	–	0/0	2/1
5: F, 48	R foot surgery	3	9/2/2	21/21	33/23	–	0	NR/NR	4/2.5
6: F, 60	L knee surgery	13	7/0/3	24/24	35/25	–	0	0/0	−1/0
7: M, 35	L ankle surgery	20	5/3/2	34/34	35/27	–	–	0/0	0/0
8: F, 45	R fingers surgery	8	5/2/3	27/25	34/24	0	0	0/0	0/0
9: F, 33	R wrist sprain	38	5/1/1	25/29	35/27	–	–	NR/NR	0/0
10: F, 33	R palm burn	4	8/2/NR	36/35	36/35	–	–	0/0	0/0
11: F, 19	R palm electrocution	13	3/0/3	25/26	35/34	–	–	2/0	0/0
12: F, 50	R brachial plexus traction	13	3/0/4.5	22/22	31/25	0	0	2/0	0/0
13: F, 42	L lumbar disc protrusion	11	8/2/8.5	21/21	34/24	–	–	2/0	2/0
14: M, 54	R ankle eversion	25	5.5/2.5/4	27/29	35/29	–	–	0/0	1/1
15: M, 26	R foot burn	5	5/2/6	26/30	34/23	–	–	0/0	0/0
16: F,42	L foot fracture, surgery	25	3/7/6	24/25	35/25	–	–	2/2	3/1
17: M, 35	R forearm crush, wrist surgery	14	5/5/5	28/28	35/32	–	–	2/2	1/2
18: F, 28	R carpal tunnel decompression	4	4/5/6	34/33	34/26	–	0	2/1	2/0
19: F, 41	R ankle sprain	2.5	8/9/8	25/24	35/26	–	–	2/0	−1/−1
20: F, 54	L thumb fracture, wrist surgery	28	7.5/4.5/5.5	33/33	35/34	–	–	0.5/0	0.5/0
21: F, 37	L ankle crush, sural nerve injury	4	8/8/7	23/25	34/23	–	0	4/0	0/0
22: F, 38	L knee sprain, surgery	54	8/7/8	22/23	36/24	0	–	0/0	1/0
23: F, 34	R knee blow, surgery	13	9/7/8	22/23	35/21	–	0	0/0	1/1.5
24: F, 15	L knee sprain	0.5	7/6/7	19/20	35/25	–	0	0/0	0/0
25: M, 42	R fifth finger crush, surgery	27	5/5/5	26/27	34/29	+	–	0/0	0/0
26: M, 29	L hand laceration	8	8/4/NR	33/32	35/25	–	–	0/0	0/0
Patients with incomplete or failed sympathetic blockade									
11: F, 19[d]	R palm electrocution	13	5/0/0	25/26	35/34	+	+	2/0	0/0
27: F, 61	L fingers crushed	14	4/0/0	34/34	35/34	–	+	3/0	0/1
28: F, 53	R radial head fracture	2	8/2/1	33/30	35/34	–	+	0/0	0/0
29: M, 22	R thumb hyperextension	35	4/1/NR	22/22	32/30	NR	+	0/0	3/0
30: F, 47	L hand surgery	20	5/3/6	30/31	32/30	+	+	3.5/2.5	2.5/1.5
31: F, 66	L 2nd finger fracture, amputation	36	8/2/8	34/34	34/34	0	+	1/6	2/0
32: F, 29	R wrist blow	72	8/7.5/7	24/26	34/30	+	+	1/0	1/2.5
33: M, 68	L sciatic nerve injury	3	5/4/6	28/31	28/30	NR	0	2/0	0/0
34: M, 53	L hand crush, shoulder sprain	9	7/5/7	30/32	34/33	0	+	0/0	0/0
35: M, 52	R carpal tunnel decompression	5	7/5/5	33/33	35/35	+	+	0/0	0/0
36: F, 52	L fourth finger fracture	9	1/2/NR	32/34	34/34	+	+	0/0	0/0

[a]Pain rating (minimal pain: 0–3; moderate pain: 4–7; severe pain: 8–10) before, 1–3 hours after, and 7 hours after sympathetic blockade.
[b]Temperature of the fingers or toes before and after sympathetic blockade in the affected and unaffected limbs.
[c]Electrodermal activity or vasoconstrictor responses were present (+) or absent (–) in the affected limb after sympathetic blockade, or were not detected on either side (0).
[d]The local anaesthetic injection was repeated two weeks after the first occasion in this patient.
EDA, electrodermal activity; F, female; L, left; M, male; NR, not recorded; R, right; VR, vasoconstrictor responses.

Procedures

Assessments were carried out in a temperature controlled laboratory or hospital ward maintained at 21 ± 1°C. Before and after sympathetic blockade, the temperature of the dorsal aspect of the middle phalanx of each finger or toe was measured with a Tempett infrared skin thermometer (Somedic Sales AB, Horby, Sweden).

Effect of startle and forehead cooling on pain ratings and autonomic activity

Skin blood flow was monitored with photoplethysmographs (Grass-Telefactor, Wet Warwick, Rhode lsland, USA) attached with Velcro straps to a finger or toe of the symptomatic and asymptomatic limbs. To detect changes in electrodermal activity (which reflects sweating), two silver–silver chloride Beckman cup electrodes (0.8 cm internal diameter) were filled with conducting paste and attached 5 cm apart on the palms or soles of the symptomatic and asymptomatic hands or feet. The voltage between each pair of electrodes was held constant at 0.5 V, and changes in current flow (reflecting changes in skin conductance from sweating) were monitored with purpose built preamplifiers based on the circuits described by Lykken and Venables.[11]

Before each stimulus, patients were prompted to rate their ongoing pain at five second intervals on a numerical rating scale, where zero corresponded to ''no pain,'' five to ''moderate pain,'' and 10 to ''extremely intense pain.'' Patients were told that pain might increase, decrease, or stay the same after each stimulus. Stimuli were presented after pain ratings had stabilised for at least 30 seconds.

The *startle stimulus* consisted of a loud tone (1000 Hz, 102 dBA, 0.5 s duration) delivered through headphones. Ratings were obtained at five second intervals for 20 seconds after stimulation, with a two to three minute gap before the next stimulus.[3]

For the *forehead cooling stimulus*, the forehead was cooled with a cylindrical copper bar (10 cm long, 0.3 cm wide, 2°C) applied lengthwise across the forehead for 25 seconds. Ratings were obtained at five second intervals during forehead cooling and for 20 seconds afterwards.[3]

The greatest increase or decrease in ratings over the 20 second interval after the tone, and over the 45 second interval during and after forehead cooling, was later investigated statistically. The startle stimulus preceded forehead cooling on 50% of occasions.

Sympathetic blockade

Patients were sedated with 30 to 70 mg of propofol intravenously. A 25 gauge needle tip was then positioned near the inferior cervical and first thoracic (stellate) ganglion on the symptomatic side under image intensifier control, or a 23 gauge needle tip was positioned near the anatomical position of the lumbar sympathetic chain, usually level with the L4 lumbar segment. Contrast agent (iohexol 300, 1 ml) was injected in all cases to exclude the possibility of intravascular or intraspinal spread of local anaesthetic agent. Once the needle tip appeared to be positioned appropriately, 5–10 ml of local anaesthetic (ropivacaine 1%) was injected.

Effects of sympathetic blockade

In each case, residual effects of sedation had disappeared before testing began. Pain ratings and vasoconstrictor and electrodermal responses to the startle stimulus were recorded 30 to 210 minutes (mean 96 minutes) after sympathetic blockade (that is, within the expected duration of local anaesthetic action). Pain ratings were also obtained during and after forehead cooling. To further confirm the presence of sympathetic blockade, limb temperatures were measured as described above.

RESULTS

Effectiveness of sympathetic blockade

Vasoconstrictor responses were considered to be minimal or absent if pulse amplitude decreased less than 20% below the level recorded immediately before the startle stimulus (corresponding to the lower quartile of responses on the unaffected side). Vasoconstrictor responses were markedly smaller or absent on the blocked side than contralaterally in 17 patients (table 1). Vasoconstrictor responses could not be detected in the unaffected limb of another 10 patients because blood vessels were already constricted before the startle stimulus. However, sympathetic blockade was considered to be effective in nine of these cases because the temperature of the fingers or toes was 6–14℃ warmer on the affected side than contralaterally (table 1). Electrodermal responses were minimal or absent in the affected limb of most patients with vascular signs of sympathetic blockade (table 1).

In each case the spread of local anaesthetic was considered adequate as judged by the spread of contrast agent under image intensifier *x* ray. Contrast agent was typically seen to flow longitudinally in close proximity to the anatomical position of the sympathetic chain. Nevertheless, sympathetic blockade appeared to be incomplete or absent in 11 cases (including one patient where signs of blockade had developed during a previous procedure). In particular, vasoconstrictor responses were detected on the affected side in all but one case. The latter patient had low blood flow in both lower limbs, and the affected side was 2℃ cooler than contralaterally (patient 33, table 1). As there was no evidence of major vessel obstruction, this finding implies inadequate sympathetic blockade.

No patient developed numbness or muscle weakness after sympathetic blockade in the distribution of the peripheral nerve or nerves that supplied the painful region. Systemic effects of local anaesthetic, suggestive of inadvertent intravenous injection, were not encountered.

Effect of sympathetic blockade on pain

Pain ratings were recorded for at least seven hours after the procedure in all but four patients. Pain relief (defined as a rating of 3 or less) continued throughout this period in nine patients with clear signs of sympathetic blockade (table 1); however, pain relief also continued in three other patients after incomplete sympathetic blockade.

Startle

The startle stimulus was not employed in two patients because of technical difficulties. Before sympathetic blockade, 17 of 34 patients (50%) reported that limb pain increased after they were startled. Pain did not change after the startle stimulus in the other 17 patients, either before or after sympathetic blockade. Sympathetic blockade generally inhibited the painful effect of startle: pain increased by (mean (SD)) 1.0 (1.1) arbitrary units (scale range 0 to 10) when patients were startled before sympathetic blockade compared with 0.2 (0.6) units afterwards ($p<0.01$, Wilcoxon test). In patients with incomplete or failed sympathetic blockade, pain increased by 1.1 (1.3) arbitrary units before the procedure compared with 0.8 (1.9) units afterwards (NS). Clear signs of sympathetic blockade were present in the affected limb of 12 patients whose pain had increased after the startle stimulus. Sympathetic blockade eliminated the painful effect of startle in nine of these patients (75%), all of whom obtained at least short term pain relief after sympathetic blockade. However, pain still increased after the startle stimulus in three patients (patients 16 to 18, table 1) with clear signs of sympathetic blockade but with minimal pain relief. Pain increased within five seconds of the startle stimulus in two of these patients and within 10 seconds of the startle stimulus in the third.

Forehead cooling

Before sympathetic blockade, 16 of 36 patients (44%) reported that pain increased in the affected limb during forehead cooling whereas pain decreased in two others. Pain increased by 0.7 (1.2) units before effective sympathetic blockade compared with 0.3 (0.7) units afterwards ($p<0.05$, Wilcoxon test). In patients with incomplete or failed sympathetic blockade, pain increased by 0.8 (1.2) units before the procedure compared with 0.5 (0.9) units afterwards (NS). Clear signs of sympathetic blockade were present in the affected limb of 12 patients whose pain had increased during forehead cooling. Sympathetic blockade eliminated the painful effect of forehead cooling in six of these patients, despite the persistence of background pain in three cases. Pain still increased during forehead cooling in the other six patients, irrespective of whether background pain had decreased (table 1).

There was no obvious association between clinical features and the effect of sympathetic blockade on spontaneous pain or pain induced by startle or forehead cooling (table 1).

DISCUSSION

Sympathetic blockade alleviates pain in only a subgroup of patients with CRPS,[4 12 13] and possibly is more effective in the early stages of the syndrome than later on.[12] From this perspective, individual variation in responsiveness to sympathetic blockade in the present series of patients is not surprising. Sympathetic blockade usually prevented the painful effect of the startle stimulus and sometimes prevented the painful effect of forehead cooling. However, it was striking that pain increased during forehead cooling and after the startle stimulus in some patients, despite clear evidence of sympathetic blockade. These findings have important implications for the mechanism of pain to sympathetically arousing stimuli in patients with CRPS.

Methodological issues

Sympathetic blockade

Various criteria have been used previously to define sympathetic blockade of the upper limb. For example,

Stevens *et al* considered that the stellate ganglion was fully anaesthetised when Horner's syndrome was present, the cobalt blue finger sweat test was negative, and the increase in finger temperature was at least 1.5℃ greater than contralaterally.[14] However, these criteria may not adequately define sympathetic blockade of the upper limb. Thus the ocular signs of Horner's syndrome can develop without vasomotor or sudomotor blockade of the upper limb.[15] Furthermore, the temperature criterion may not be stringent enough to define sympathetic blockade. For example, Shürman *et al*[16] reported that digital vasoconstrictor responses persisted after sympathetic blockade in 48% of patients who met the temperature criterion employed by Stevens *et al*.[14]

The principal criterion for effective sympathetic blockade in our study was the abolition of vasoconstrictor responses in the blocked limb during sympathetic arousal, with the persistence of these responses contralaterally. This criterion could not be applied to 10 of 36 patients (28%) owing to low skin blood flow in the asymptomatic limb. However, sympathetic blockade appeared to be effective in nine of these cases because electrodermal responses were abolished and the fingers or toes of the affected limb were warmer than on the opposite side by 6–14℃. Digital temperature remained more than 2℃ below core body temperature in 10 of 26 patients with clear signs of sympathetic blockade, presumably because of the cool ambient temperature or because of residual sympathetic activity. We did not measure sympathetic activity in the muscle or bone of the affected limb after sympathetic blockade. However, this was likely to be minimal because the sympathetic supply of these tissues separates from the supply of the skin in the limb rather than in the sympathetic chain.[17]

Sympathetic blockade of the upper limb was incomplete or failed in 10 of 22 cases and lumbar sympathetic blockade failed in one of 15 cases, despite radiological confirmation that the needle tip was at the required location. This may have been a result of individual variation in the anatomy of the sympathetic chain, particularly in the upper thoracic region. For example, sympathetic fibres that supply the upper limbs sometimes synapse in the second and third thoracic sympathetic ganglia and join the brachial plexus directly, thus bypassing the stellate ganglion.[15] However, the stellate ganglion was targeted for blockade rather than the T2–3 sympathetic ganglia, to minimise the risk of pneumothorax.

Non-specific effects of sympathetic blockade

Investigating the effect of sympathetic blockade on pain and other sensory disturbances in CRPS is complicated by the possibility of placebo effects, parallel decreases in anxiety and pain, inadvertent somatic blockade, and systemic uptake of the local anaesthetic agent. Although effects such as these may influence pain ratings shortly after sympathetic blockade, non-specific effects do not seem to account for persistent pain relief.[18 19] In the present study, pain relief for at least seven hours was experienced by nine of 24 patients with indisputable signs of sympathetic blockade, but was also reported by three of nine patients after incomplete or failed sympathetic blockade. Thus a non-specific effect of the procedure was apparently therapeutic in some cases. This was exemplified by one of our patients who showed signs of sympathetic blockade on one occasion but not when the procedure was repeated two weeks later, but nevertheless the pain relief was greater on the second occasion. In the substantial number of patients who experienced little pain relief after sympathetic blockade, chronic inflammation, sensitisation of nociceptive afferents, sensitisation of spinal pain transmission neurones, or faulty higher order processing of nociceptive impulses may have influenced pain.[13 20]

Effect of sympathetic blockade on pain induced by startle and forehead cooling

We expected that sympathetic blockade would prevent increases in pain evoked by sympathetic activation in CRPS patients. The painful effect of the startle stimulus disappeared in patients who experienced pain relief after sympathetic blockade, and the painful effect of forehead cooling also subsided in some cases. This is consistent with a reduction in adrenergic excitation of a nociceptive focus[21–26] in the affected limb of patients with CRPS.[7–9] Crosstalk between sympathetic efferent and sensory afferent fibres may also be a source of pain and abnormal sensations in patients with post-herpetic neuralgia[27] and other forms of peripheral nerve injury.[28 29] In addition, the nociceptive discharge resulting from peripheral sensory–sympathetic interaction could sensitise central pain transmission neurones and mediate allodynia to light tactile stimulation in patients with neuropathic pain.[27]

One of the most intriguing findings to emerge from this study was the persistence of pain evoked by the startle stimulus in patients whose spontaneous pain remained unchanged after sympathetic blockade. Patients whose spontaneous pain persisted after effective sympathetic blockade would be considered to have ''sympathetically independent pain.''[4] However, this term does not seem to be appropriate for patients whose pain is aggravated by sympathetically arousing stimuli, and may need to be revised. Our findings also show that an increase in pain during sympathetically arousing stimulation does not necessarily indicate pain relief after sympathetic blockade, thus complicating the notion of ''sympathetically maintained pain.'' Defining ''sympathetically maintained pain'' in terms of a reduction in pain after sympathetic blockade fails to take into account non-specific effects of sympathetic blockade. Perhaps the most direct way to identify a peripheral adrenergic component of pain would be to investigate nociceptive responses to local injection of adrenergic agonists and antagonists,[7–9] preferably in double blind, placebo controlled trials.

Pain usually peaked within five to 10 seconds of the startle stimulus.[3] As substances take around 10 seconds to move from the venous to the arterial side of the circulation and another 10 to 20 seconds for the arterial concentration to peak,[30] catecholamines released into the circulation from elsewhere in the body do not account for the increase in pain. Furthermore, the painful response to startle and forehead cooling remained unchanged in one of our patients after partial α adrenergic blockade with phenoxybenzamine. Pain may have increased during and after stimulation because of a sudden movement or an increase in muscle tension, but in most cases there was no obvious sign of movement on physiological recordings.

Deafferentation of central pain transmission neurones or disinhibition of these neurones or their rostral targets appears to contribute to pain in patients with various forms of neuropathic pain (for example, post-herpetic neuralgia, spinal cord injury, and thalamic lesions).[31–33] One of the hallmarks of pain in the thalamic syndrome is that emotional disturbances and stimulation of the special senses (for example, loud or unexpected noises) can intensify pain. Furthermore, noxious stimulation (particularly intense cold) anywhere on the affected side of the body can provoke widespread hyperalgesia.[33] In the present study, pain to the startle stimulus and forehead cooling persisted in patients whose spontaneous pain remained unchanged after sympathetic blockade. In addition, pain that had subsided after sympathetic blockade could sometimes be rekindled by cooling the forehead. In combination, these observations suggest that a central mechanism might contribute to

stimulus evoked pain in CRPS.[34] It is interesting that thalamic perfusion is greater contralateral than ipsilateral to the affected limb during the first seven months of CRPS, presumably in association with increased nociceptive traffic, whereas contralateral thalamic perfusion decreases below ipsilateral perfusion in chronic CRPS.[35] The functional implications of these changes in thalamic perfusion require further investigation.

Pain itself and emotions such as fear strongly activate pain modulation circuits that descend from the periaqueductal grey matter and brain stem adrenergic and serotoninergic nuclei.[36] Apart from their role in pain modulation, these midbrain and brain stem nuclei are involved in central autonomic control, affective behaviour, and cortical arousal and awareness.[37 38] Persistent mobilisation of inhibitory pain modulation circuits in people with chronic pain appears to deplete opioid reserves involved in descending pain control.[39] Consequently, facilitatory influences on spinal nociceptive discharge[40] could outweigh inhibitory opioid influences in chronic pain states such as CRPS. Van Bockstaele *et al* suggested that inhibitory opioid influences in the locus coeruleus mediate passive coping behaviours to inescapable stress and pain.[41] The fatigue of this inhibitory influence might potentiate arousal responses and nociceptive transmission in the thalamus and cortex. Importantly, projections from brain stem adrenergic nuclei, which mediate cortical arousal, also facilitate nociceptive transmission in the thalamus.[42] Thus if inhibitory pain modulation fails, activation of brain stem adrenergic nuclei during emotional reactions, heightened states of arousal, or sympathetic regulatory control could intensify pain.

Conclusions

It has generally been assumed that sympathetic neural discharge provokes pain in CRPS by aggravating inflammation or by exciting adrenoceptors on sensory nerves in the affected limb. However, our findings suggest that sympathetically arousing stimuli also act on a central process to exacerbate pain in some patients, independent of the peripheral sympathetic nervous system. If so, central as well as peripheral sympathetic mechanisms could contribute to pain and hyperalgesia during sensory stimulation and emotional arousal in patients with CRPS.[1–4]

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